Efficacy Review

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Products: Sergeant's Fipronil + Etofenprox + Methoprene Spot-on for Cats

EPA Reg. #: 2517-RUL

A.I.'s: Fipronil (9.8%), Etofenprox (15.0%), Methoprene (11.8%)

Decision #s: 442446

DP #s: 385126

Submission: R310, New Products, RD Science Review

MRIDs: Submitted: 48302110, 48302111, 48302112, 48302113, 48302114

Cited: Selective Cite-All for efficacy (Merial)

GLP: No

MRID 48302110

Title: Immediate Efficacy of a Combined Application of Frontline Plus with Etofenprox as a Squeeze-on against Fleas (*Ctenocephalides felis*) and Ticks (*Dermacentor variabilis*) on Cats.

Guideline: OPPTS 810.3300

Materials and Methods: A laboratory study was conducted with an experimental formulation, with etofenprox (12.6%) added to a registered fipronil + s-methoprene pet product. Etofenprox technical was added to Merial's Frontline Plus (65331-4), with dosages applied in accordance with the parent product label. Cats receiving the experimental formulation received a 0.58 mL dosage, regardless of cat body weight. 18 cats, provisioned with cone collars, were allocated to 3 groups (control, experimental formulation, and positive control). One day prior to treatment, cats were infested with 100 fleas and 50 ticks (*Dermacentor*), with subsequent weekly reinfestation on days 8, 15, 22, and 28 after treatment. Flea and tick counts were taken at 1 and 4 hours after application on the day of treatment, and similarly after reinfestation on days 8, 15, 22, and 28 to measure speed of kill, as evidence of repellency. Counts were also made at 24 and 48

hours after treatment and after each re-infestation on days 1, 2, 9, 10, 16, 17, 23, 24, 29, and 30. Fleas and ticks were not removed or destroyed until the last count in each re-infestation cycle, which was done by comb removal. Effiacy was calculated using Abbott's formula.

Study Summary of the Results:

1. Efficacy against both fleas and ticks exceeded 90% for the duration of the efficacy study, 30 days after treatment.

Entomologist's Observations/Discussion:

1. The 1-4 hour efficacy evaluations are suitable for evaluating claims of 'quick acting', but are not appropriate for evaluating repellence. For repellence to be demonstrated, a study would have to be done to demonstrate 90% reduction in tick attachment/retention.
2. 1 hour efficacy data indicates that the formula containing etofenprox starts killing fleas and ticks within one hour at a higher level than the formula with fipronil alone.

MRID 48302111

Title: Immediate Efficacy of a Combined Application of Frontline Plus with Etofenprox as a Squeeze-on against Fleas (*Ctenocephalis felis*) and Ticks (*Dermacentor variabilis*) on Cats.

Guideline: OPPTS 810.3300

Materials and Methods: Etofenprox was added to Frontline plus at 12.6% for immediate efficacy evaluations. Etofenprox technical was added to Merial's Frontline Plus (65331-4), with dosages applied in accordance with the parent product label. Cats receiving the experimental formulation received a 0.58 mL dosage, regardless of cat body weight. 9 cats, provisioned with cone collars, were allocated to 3 groups (control, experimental formulation, and positive control). One day prior to treatment, cats were infested with 100 fleas and 50 ticks (*Dermacentor*), with subsequent weekly reinfestation on days 8, 15, 22, and 28 after treatment. Flea and tick counts were taken at 1 and 4 hours after application on the day of treatment, and similarly after reinfestation on days 8, 15, 22, and 28 to measure speed of kill, as evidence of repellency. Counts were also made at 24 and 48 hours after treatment and after each re-infestation on days 1, 2, 9, 10, 16, 17, 23, 24, 30, and 31. Fleas and ticks were not removed or destroyed until the last count in each re-infestation cycle, which was done by comb removal. Effiacy was calculated using Abbott's formula.

Study Summary of the Results:

1. Flea efficacy on day of treatment was significantly higher for the treatment including etofenprox than fipronil alone (25% vs. 0% at 1 hour post-treatment, and 88% vs. 14% at 4 hours post-treatment). Tick efficacy on the day of treatment was

significantly higher for the etofenprox treatment at 4 hours after application (53% vs. 0%).
2. Mean efficacy against fleas exceeded 90% when assessed at 1-2 days after treatment or reinfestation with parasites, through 17 days after treatment.
3. Mean efficacy against ticks exceeded 90% when assessed at 1-2 days after treatment or reinfestation with parasites through 31 days after treatment.

Entomologist's Observations/Dicussion:

1. The 1-4 hour efficacy evaluations are suitable for evaluating claims of 'quick acting', but are not appropriate for evaluating repellence. For repellence to be demonstrated, a study would have to be done to demonstrate 90% reduction in tick attachment/retention.
2. 1-4 hour efficacy data indicates that the formula containing etofenprox starts killing fleas and ticks within four hours at a higher level than the formula with fipronil alone.

MRID 48302112

Title: Dose Titration with S-Methoprene Squeeze-On Cats Measuring Flea Egg Sterilization

Guideline: OPPTS 810.3300

Materials and Methods: A laboratory dose titration study was conducted to evaluate (and project) the residual protection time for cats treated with varying dosages of s-methoprene. Prevention of larval development, pupation, and adult flea emergence was evaluated, with dose rates ranging from 2.1 to 130.8 mg/kg body weight. Six treatment groups were established with 2 cats each, and 6 additional cats were assigned to an untreated control group. Cats were fitted with Elizabethan collars to prevent grooming and pest removal Cats were infested with fleas 1 day after treatment, and reinfested once weekly thereafter. Drop pans were used to collect flea eggs on the 2nd and 6th day after each infestation. Eggs were sorted and incubated for 3 days to measure fertility. Other eggs were incubated on a flea growing medium for 21-35 days to evaluate flea emergence. % hatch and % adult development were calculated for each cat. Efficacy (compared to controls) was calculated using Abbott's formula. Efficacy was plotted against dosage to develop a regression equation, used to determine the relationship between dosage and duration of residual flea ovisterilant efficacy using regression analysis.

Study Summary of the Results:

1. Progressive failures in preventing egg hatch occurred after the 14th day, with the lowest rates.
2. Based on inhibition of adult flea emergence, the analysis supports a claim for up to 4 months for smaller cats, and no less than 1 month for large cats.

Entomologist's Observations/Discussion:

1. A claim against flea eggs and larvae and breaking of the flea life cycle is supported for 'up to 4 months'.

MRID 48302113

Title: Comparative efficacy evaluation of Sergeant's squeeze-on and Frontline Plus for the treatment of adult cat flea (*Ctenocephalis felis*) and Tick (*Haemaphysalis elliptica, Rhipicephalus turanicus*, and *Dermacentor variabilis*) infestations on cats.

Guideline: OPPTS 810.3300

Materials and Methods: Etofenprox was added to Frontline plus at 15.0% for efficacy evaluations on cats. 7 treatment groups were evaluated, including an untreated control, and 2 rates each of FrontLine Plus (Fipronil + S-methoprene), Sergeant's 1 (Fipronil + S-methoprene), and Sergeant's 2 (Fipronil + S-methoprene + Etofenprox). The 2 rates of the experimental treatments were 0.5 mL and 0.055 mL of each treatment. 42 cats, ranging in weight from 5-15 lbs, were provisioned with cone collars, and allocated randomly to the 7 groups (6 cats per group) Cats were all qualified for health and parasite retention. 50 ticks were placed at various times during the study. *D. variabilis* were used on days -6, -1, 21, and 28. *R. turanicus* were used on day 7. *H. elliptica* were used on day 14. Infestations of 100 fleas were made on days -6, -1, 7, 14, 21, and 28. 1 and 4 hour in situ assessments were made on the day of placement for each parasite. 24 and 48 hour assessments were made one and two days after the placement for all parasites. Fleas and ticks were not removed or destroyed until the last count in each re-infestation cycle, which was done by comb removal. Effiacy was calculated using Abbott's formula.

Study Summary of the Results:

1. Mean efficacy against ticks exceeded 90% when assessed at 1 day after reinfestation at 28 days post treatment, with the exception of *H. elliptica*, but efficacy exceeded 90% for all species when evaluated at 2 days after reinfestations. The lower rates did not demonstrate adequate efficacy.
2. Mean efficacy against fleas exceeded 90% when assessed at 2 days after treatment and reinfestations, for both treatment rates.
3. Immediate efficacy on fleas (i.e. kill/repellence within 4 hours of treatment) ranged from 0-75% for 1-4 hours immediately after treatment. With reinfestations after 7, 14, 21, 28, and 35 days from treatment, efficacy exceeded 90% within 4 hours for all only the 7 day reinfestation. Efficacy did not exceed 90% within 4 hours for reinfestations on days 14, 21, 28, or 35 days after treatment.
4. Immediate efficacy on ticks ranged from 11-71% for 1-4 hours immediately after treatment. With reinfestations after 7, 14, 21, and 28 days from treatment, efficacy exceeded 90% within 4 hours for only the 7 day reinfestation. Efficacy did not exceed 90% within 4 hours for reinfestations on days 14, 21, 28, or 35 days after treatment.

Entomologist's Observations/Dicussion:

1. Efficacy against fleas and ticks was adequate to support controls claims through 30 days for the squeeze-on product containing etofenprox, applied at a label rate of 0.5 mL per cat.

MRID 48302114

Title: Comparative efficacy evaluation of Sergeant's Squeeze-on and Frontline Plus for the treatment of adult cat flea (*Ctenocephalides felis*) and tick (*Haemaphysalis elliptica, Rhipicephalus turanicus,* and *Dermacentor variabilis*) infestations on cats.

Guideline: OPPTS 810.3300

Materials and Methods: Etofenprox was added to Seargeant's Fipronil-Methroprene formulation Frontline plus at the rate of 15% for efficacy evaluations. This treatment was compared to a 2 positive controls, Merial's Frontline Plus and a Sergeant's Fipronil + s-methoprene combo, and an untreated control. The 3 treatments were split whereby one group received a full label dose, while ther second group received a dosage based on a titration from the largest animal (20lbs cat) dose, to simulate the lightest possible dosage according to label directions. Each group consisted of 6 animals. These treatments were evaluated for efficacy against pre-existing fleas and ticks (*Dermacentor variabilis*). Residual efficacy was measured against *R. turanicus*, *H. elliptica,* and *D. variabilis* over 30 days following treatment. Cats were infested with 100 fleas and 50 ticks one day before treatment, and again at 7, 14, 21, and 28 days after treatment. Counts were made at 1 and 4 hours post treatment and also after every reinfestation—this was to measure speed of kill and/or repellency. Counts were also made at 24 and 48 hours after initial infestation and all re-infestations. Flea counts were only made at 48 hours after treatment and each re-infestation. Mortality was calculated using Abbott's formula. For speed of kill/repellence, the number of killed/repelled fleas on the liner below each treated cat was divided by the total number of fleas placed on the cat (all x 100), adjusted for 'normal' attrition on control dogs.

Study Summary of the **Results:**

1. Mean efficacy against fleas exceeded 90% when assessed at all assessment times up to 30 days after treatment.

Entomologist's Observations/Discussion:

1. Efficacy against fleas and ticks was adequate to support controls general claims through 30 days (one month) after treatment.
2. No immediate efficacy claims (i.e., within 1-4 hours of application or reinfestation by parasites) are supported by this data.

Overall Review of Label Claims and Directions:

-killing claims against flea pupae are unsupported and thus, unacceptable
-repellence claims against ticks are unsupported and thus, unacceptable

Based upon submitted efficacy data, claims for the product to start working within 1 hour, or within hours are acceptable.

Claims supported by selective and cite-all methods:
-kill claims against fleas, flea eggs & larvae, ticks, including those that may transmit Lyme disease, chewing lice, and mosquitoes
-fast acting
-long-lasting
-waterproof
-description of product spread over pet's skin/hair
-prevents all flea stages (eggs, larvae, pupae) from developing
-stops existing infestations and prevents establishment of new infestations
-kills fleas which may cause flea allergy dermatitis
-kills all stages of ticks (larva, nymph, and adult), including deer ticks, brown dog tick, American dog tick, and Lone Star tick.
-kills ticks that may transmit Lyme disease, Rocky Mountain spotted fever, erlichosis, and other tick-borne diseases
-rapidly minimizes chewing lice infestations
-kills mosquitoes
-When used monthly, xxxx breaks the flea life cycle and controls ticks and chewing lice infestations. Do not reapply for 30 days.
-Controls fleas for up to 6 weeks.
-Kills mosquitoes within 24 hours for up to 14 days, and within 48 hours for up to 28 days with a monthly application
-keeps working even if the cat gets wet
-fleas, ticks, and chewing lice are killed quickly after coming into contact with a treated cat. Fleas and ticks do not need to bite the cat in order to die.

Line by Line Review of Label Claims

Mosquitoes. Kills mosquitoes: Acceptable

Adult Fleas. Studies show that [brand name] kills adult fleas for up to six weeks: Acceptable, but strike the statement "studies show".

Kills Fleas [Up to[4][6] weeks]!: Acceptable

Kills Fleas that may cause flea allergy dermatitis, flea bite anemia, and tapeworm infestation: Acceptable

Stops and prevents reinfestation: Acceptable

Controls flea reinfestation for up to [six weeks]: Acceptable

[brand name] kills adult fleas for up to six weeks: Acceptable

If cat is a high risk for flea reinfestation a once month application may be needed: Acceptable

Dual Action [!]: Fipronil and Etofenprox Effectively Breaks the Flea Life Cycle: Unacceptable, as the life cycle claim is driven by s-methoprene efficacy.

Prevents and controls reinfestations: Acceptable

Flea Eggs and Larvae: Acceptable

Stops and prevents infestations: Acceptable

Controls flea reinfestation for up to 6 weeks: Acceptable

Research demonstrates that [brand name] kills adult fleas, flea eggs, flea larvae and pupae for up to six weeks: Pupae claim is unacceptable. Pupal development is prevented by treatment, but the product was not shown to actually kill pupae directly.

[brand name] prevents development of all flea stages for up to 6 weeks: Acceptable

Prevents all flea stages (adult fleas, flea eggs, flea pupae, and flea larvae): Acceptable

If cat is a high risk for flea reinfestation a once month application may be needed: Acceptable

Kills flea eggs [larvae][pupae] for up to [3 months][12 weeks]: Pupae claim is unacceptable. Pupal development is prevented by treatment, but the product was not shown to actually kill pupae directly.

With (s)-methoprene Insect Growth Regulator which Breaks the Flea Life Cycle: Acceptable

With (s)-methoprene to Break Flea Life Cycle: Acceptable

With Insect Growth Regulator to Break Flea Life Cycle: Acceptable

Triple Action [!]: Fipronil and Etofenprox with (s)-methoprene IGR effectively breaks the flea life cycle: Acceptable

Triple Action [!]: Effectively Breaks the Flea Life Cycle[!]: Acceptable

Kills all stages of the flea life cycle: Acceptable

Kills Flea Eggs & Flea Larvae for [(up to 3 months)!]: Acceptable

Prevents Flea Eggs From Developing Into Biting Adults: Acceptable

Prevents and controls reinfestations: Acceptable

Ticks: Acceptable

Kills Ticks including those that may transmit Lyme disease: Acceptable

Kills Ticks for Up to [4 weeks]!: Acceptable

Kills Deer Ticks (vector of Lyme Disease) for up to 4 weeks: Change parenthetical statement to "which may transmit Lyme Disease".

Kills Ticks (Including Deer Ticks) for up to 4 weeks: Acceptable

Kills [and repels][American Dog Ticks for up to 4 weeks]: Repels statement is unacceptable, kill claim is acceptable

Kills [Brown], [American][and Lone Star} dog ticks for up to 4 weeks: Acceptable

Kills [& Repels] American Dog Ticks [(*Dermacentor variabilis*)] for up to 4 weeks: Repels statement is unacceptable, kill claim is acceptable

Multiple Infestations:

(Brand Name) provides convenient and effective flea, tick, chewing lice and mosquito control for cats and kittens: Acceptable

Controls reinfestation for up to 4 weeks: Acceptable

Flea & Tick Control for Cats & Kittens 12 weeks old and older: Acceptable

Kills fleas, ticks, chewing lice & mosquitoes: Acceptable

Kills fleas, ticks, mosquitoes, and (chewing) lice: Acceptable

Monthly flea, tick, mosquito and lice protection: Acceptable

Kills fleas, ticks, mosquitoes, and lice: Acceptable

[Four][4] Way Protection: Acceptable

[4 Week] [Flea and Tick & Treatment!]: Acceptable

[Four (4) Week][Flea, Tick, Mosquito and Lice control]: Acceptable

When used monthly [brand name] completely breaks the life cycle and controls tick and chewing lice infestations: Acceptable

4 week Flea and Tick Treatment!: Acceptable

Once A Month Flea and Tick Treatment: Acceptable

Kills Fleas and Ticks for up to 4 weeks!: Acceptable

Starts to kill fleas and ticks in an hour, continues to kill for a month: Acceptable

Kills [93% of fleas] in 4 hours [and] [98 to 100% of tick] in one hour: Explicit percentage claims are unacceptable and must be removed.

Research shows that [Brand Name] kills 93% of fleas in 4 hours and 98% to 100% of Dermacentor ticks in one hour: Explicit percentage claims are unacceptable and must be removed.

Kills more than 50% of ticks in 1 hour: Explicit percentage claims are unacceptable and must be removed.

Kills 100% of fleas and ticks in [24 hours][1 day]: Explicit percentage claims are unacceptable and must be removed.

Starts killing fleas and ticks in as little as 1 hour: Acceptable

Stops and prevents infestations: Acceptable

Fast Acting: Acceptable

Cats can be bathed 24 hours after treatment: Acceptable

Waterproof: Acceptable

Long Lasting: Acceptable

Once a month treatment recommended: Acceptable

A once monthly application is recommended for chewing lice: Acceptable

Fast Action against chewing lice infestations: Acceptable

[brand name] contains Fipronil, Etofenprox and the insect growth regulator (IGR) (s)-methoprene to effectively kills fleas, ticks, mosquitoes and chewing lice. The active ingredients

in [brand name] work by collecting in the hair follicles and skin oils. This product features a sustained-release formula that discharges from the cat's hair follicles using the natural skin oils, resulting in fast-acting [and long-lasting] control of fleas, ticks, mosquitoes and chewing lice [for 30 days]. [Diagram with visual of Fipronil, Etofenprox and Nylar IGR collecting and being released from hair follicle]: Acceptable

FREQUENCY OF APPLICATION

Use [brand name] monthly for complete control of flea, tick [and] chewing lice [and mosquito] infestations. [Studies show that][brand name] kills fleas for up to six weeks, and flea eggs, flea larvae, and flea pupae for up to 4 months.

If your pet is high risk for flea reinfestation [, or in a highly infested environment], apply monthly. Apply monthly to control ticks, mosquitoes and chewing lice. [Brand Name] kills mosquitoes within 24 hours for up to 14 days, and within 48 hours for up to 28 days. [Brand name] remains effective, even after bathing, water immersion, or exposure to sunlight. Allow treated area to dry thoroughly. Do not reapply for 30 days: The statement "studies show" and claim against 'flea pupae' must be removed. The remainder of the claim is acceptable.